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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,298	02/08/2000	JUNKO YAMAMOTO	1422-411P	1749

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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/485,298	Yamamoto et al.
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 17, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *20, 21, 23, 24, 26-28, 30-32, 34, 35, and 37-41* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *20, 21, 23, 24, 26-28, 30-32, 34, 35, and 37-41* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 17, 2003 has been entered.

Specification

2. Claims 22, 25, 29, 33, and 36 have been canceled without prejudice towards further prosecution. Claims 20, 23, 27, 31, and 34 have been amended.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 20, 21, 23, 24, 27-28, 31-32, 34, 35, and 37- 41 are rejected under 35 U.S.C 103 (a) over Huse et al. (U.S. Patent 5,681,726) (October 28, 1997) in view of Gelfand et al. (U.S. Patent 5,939,292) (August 17, 1999) further in view of Frye et al. (U.S. Patent 6,008,041) (December 28, 1999).

Huse et al teach a method and kit for amplifying a DNA by polymerase chain reaction by the use of a DNA fragment comprising a nucleotide analog as a template (Claim 8, Figure 1, and Column 12, lines 25-31).

Huse et al teach a method for amplifying a DNA characterized in that the DNA fragment is a cDNA prepared by reverse transcription reaction using an RNA as a template (Claim 8, Figure 1, and Column 12, lines 25-31).

Huse et al teach at least one nucleotide analog to be incorporated in place of dGTP, dCTP, dATP, and dTTP and a reagent for synthesizing in the presence of a nucleotide analog a cDNA that is complementary to an RNA (Claim 8, Figure 1, and Column 12, lines 25-31).

Huse et al do not teach the nucleotide analogs that do not cause termination of the DNA amplification.

Gelfand et al. teach the nucleotide analogs that do not cause termination of the DNA amplification (Abstract and Examples I-X and claims 1-13).

Huse et al do not teach the method for amplifying a DNA in the presence of two or more kinds of nucleotide analogs, wherein the nucleotide analogs are uniformly incorporated into the resulting DNA, thereby selectively amplifying DNA of a target sequence.

Gelfand et al teach the method for amplifying a DNA in the presence of two or more kinds of nucleotide analogs, wherein the nucleotide analogs are uniformly incorporated into the resulting DNA, thereby selectively amplifying DNA of a target sequence (Examples I-X).

Huse et al do not teach a kit containing thermostable DNA polymerase.

Gelfand et al. teach a kit containing thermostable DNA polymerase (Abstract and Examples I-X and claims 1-25).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method for amplifying a DNA in the presence of two or more kinds of nucleotide analogs that do not cause termination of the DNA amplification and a kit containing thermostable DNA polymerase of Gelfand et al with the methods of amplifying nucleic acids using modified nucleotide template of Huse et al ., since Gelfand et al state, "Modified thermostable DNA polymerases having enhanced efficiency for incorporating unconventional nucleotides, such as ribonucleotides, into DNA products, are advantageous in many in vitro synthesis applications. Such enzymes are particularly useful for use in nucleic acid sequencing protocols and provide novel means for DNA sequence analysis. Genes

encoding the modified enzymes and methods for their production and use offer cost and efficiency advantages for DNA sequencing (Abstract)". An ordinary artisan would have been motivated by these express statements of Gelfand et al to substitute and combine the method for amplifying a DNA in the presence of two or more kinds of nucleotide analogs that do not cause termination of the DNA amplification and a kit containing thermostable DNA polymerase of Gelfand et al with the methods of amplifying nucleic acids using modified nucleotide template of Huse et al , in order to achieve the express advantages of modified nucleotide analogues, as noted by Gelfand et al , which provides genes encoding the modified enzymes and methods for their production and use that offer cost and efficiency advantages for DNA sequencing and provides modified thermostable DNA polymerases having enhanced efficiency for incorporating unconventional nucleotides, such as ribonucleotides, into DNA products, that are advantageous in many in vitro synthesis applications.

Huse et al. in view of Gelfand et al do not teach the method, wherein nucleotide analogs are selected from 7-deaza-dGTP.

Frye et al. teach the method, wherein nucleotide analogs are selected from 7-deaza-dGTP (Example 1, Column 25, lines 28-42).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method, wherein nucleotide analogs are selected from 7-deaza-dGTP of Frye et al. with the methods of amplifying nucleic acids using modified nucleotide template of Huse et al. in view of Gelfand et al., since Frye et al state, "The

application of 7-deaza-dGTP has been shown to eliminate some of the nonspecific background while it has no effect on the Taq DNA polymerase itself (Column 25, lines 38-40)". An ordinary artisan would have been motivated by these express statements of Frye et al. to substitute and combine the method, wherein nucleotide analogs are selected from 7-deaza-dGTP of Frye et al. with the methods of amplifying nucleic acids using modified nucleotide template of Huse et al. in view of Gelfand et al., in order to achieve the express advantages, as noted by Frye et al , of the application of 7-deaza-dGTP, which has been shown to eliminate some of the nonspecific background while it has no effect on the Taq DNA polymerase itself.

5. Claims 26 and 30 are rejected under 35 U.S.C. 103 (a) over Huse et al. (U.S. Patent 5,681,726) (October 28, 1997) in view of Gelfand et al. (U.S. Patent 5,939,292) (August 17, 1999) further in view of Frye et al. (U.S. Patent 6,008,041) (December 28, 1999) further in view of Dodge et al. (U.S. Patent 5,912,117) (June 15, 1999).

Huse et al in view of Gelfand et al. further in view of Frye et al. teach the method of claims 20, 21, 23, 24, 27-28, 31-32, 34, 35, and 37- 41 as described above.

Huse et al in view of Gelfand et al. further in view of Frye et al. do not teach the compounds for lowering the *Tm* value of a double-stranded nucleic acid.

Dodge et al teach the compounds (glycerol and DMSO) for lowering the *Tm* value of a double-stranded nucleic acid.(Column 8, line 49 to column 9, line 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the compounds for lowering Tm of duplex

DNA of Dodge et al with the fast and accurate methods of amplifying nucleic acids using modified nucleotide template and nucleotides of Huse et al in view of Gelfand et al. further in view of Frye et al., since Dodge et al state, "To assure PCR efficiency, glycerol and other related solvents such as dimethyl sulfoxide, can be used to increase the sensitivity of the PCR at the amplification level and to overcome problems pertaining to the sequencing of regions of DNA having strong secondary structure. These problems may include : (1) low efficiency of the PCR, due to a high frequency of templates that are not fully extended by the polymerizing agent or (2) incomplete denaturation of the duplex DNA at high temperatures, due to high GC content. The use of such solvents increases the sensitivity of the assay at the level of amplification to approximately several femtograms of DNA (which is believed to correspond to a single spirochete cell). This level of sensitivity eliminates the need to detect amplified target DNA using a probe, and thereby dispenses with the requirements for radioactive probes, gel electrophoresis, Southern blotting, filter hybridization, washing and autoradiography (Column 8, line 49 to column 9, line 2)". An ordinary artisan would have been motivated by these express statements of Dodge et al to substitute and combine the compounds for lowering Tm of duplex DNA of Dodge et al with the fast and accurate methods of amplifying nucleic acids using modified nucleotide template and nucleotides of Huse et al in view of Gelfand et al. further in view of Frye et al., in order to achieve the express advantages of solvents, as noted by Dodge et al , which provides assurance of PCR efficiency and increases the sensitivity of the PCR at the amplification level to overcome problems pertaining to the sequencing of regions of DNA having strong secondary structure

including : (1) low efficiency of the PCR, due to a high frequency of templates that are not fully extended by the polymerizing agent or (2) incomplete denaturation of the duplex DNA at high temperatures, due to high GC content and in addition, increases the sensitivity of the assay at the level of amplification to approximately several femtograms of DNA (which is believed to correspond to a single spirochete cell) which eliminates the need to detect amplified target DNA using a probe, and thereby dispenses with the requirements for radioactive probes, gel electrophoresis, Southern blotting, filter hybridization, washing and autoradiography.

Response to Amendment

6. In response to amendment, previous 103 (a) rejections have been withdrawn. However, new 103 (a) rejections have been included.

Response to Arguments

7. Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 746-4979.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

April 3, 2003

ARUN K. CHAKRABARTI
PATENT EXAMINER